Clinical Review

Infection With the Human T-Lymphotropic Virus Type I
A Review for Clinicians

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The human T-cell lymphotropic virus type I (HTLV-I) is the first retrovirus identified in humans. It has been responsible for a number of clinical syndromes, most notably adult T-cell leukemia or lymphoma and tropical spastic paraparesis. In the United States, infection with this virus is most frequently found in specific subsets of our population, particularly in those who live in the southeastern states, have southern Japanese ancestry, or share intravenous drug paraphernalia. Understanding the epidemiology and clinical manifestations of this virus is necessary to properly diagnose and care for patients with HTLV-I infection.

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Although still uncommon in many parts of the United States, infection with the human T-cell lymphotropic virus type I (HTLV-I) has been identified in immigrants from endemic areas; blacks and Native Americans from the southeastern United States; and, with increasing frequency, in intravenous drug users. In Hawaii, antibodies to the virus and those diseases related to viral infection are found predominantly in the Japanese population and, in particular, in those whose ancestors immigrated from southern Japan. For physicians practicing among patients from these high-risk groups, HTLV-I infection and its associated disease states will present an increasing challenge. These physicians will not only need to be familiar with the virus and its associated diseases but will also be challenged with the responsibility of influencing the rate at which the virus spreads throughout the United States and the world.

We review the virus and the means by which it is spread and manifests disease states. In addition, we address several methods by which practicing physicians can influence the spread of this virus.

HTLV-I Virus

The HTLV-I virus was the first of several retroviruses identified in humans (Table 1). It was initially isolated in 1978 by Gallo and Poiesz from the T lymphocytes of a patient with a cutaneous T-cell lymphoma.[1,2] Since that time the virus has been associated etiologically with adult T-cell leukemia or lymphoma (ATL) but only occasionally with the malignant neoplasms from which it was first isolated.

The HTLV-I virus is a type C retrovirus. Being an RNA tumor virus, it depends on the enzyme reverse transcriptase for its replication. This enzyme uses the viral RNA as a template for the production of DNA, which then randomly integrates into the chromosomal DNA of the host cell. Once there, viral replication occurs by using the cell's own synthetic machinery, producing new virions containing viral RNA, as well as those proteins responsible for the packaging of these virions (Figure 1).

The clinical course of HTLV-I infection is related predominantly to its effects on the T lymphocyte. The virus preferentially attacks the $CD4^+$ or helper T lymphocyte. Once inside a T cell, the provirus is randomly integrated into the cellular genome. Thus, polyclonal proviral integration is found in peripheral blood lymphocytes. When progression to ATL occurs, the virus is found only in a monoclonal pattern (Figure 2).

The location of the monoclonal HTLV-I provirus integration is different for each patient with ATL. It does not appear that HTLV-I provirus need be present in a single location for it to be leukemogenic, as occurs with other viruses with the potential to create malignant disorders. Its capacity for leukemogenesis is thought to be related to the presence of a gene, called *tax* (analogous to the human immunodeficiency virus's *tat*) for transactivation factor, within the viral genome. The *tax* gene appears to induce the production of interleukin-2 and its receptors and may therefore initiate abnormally rapid autologous cellular growth (Figure 3).

Recent work has shown that cell lines containing *tax* are able to be passed from generation to generation in mice and have the ability to convey malignant potential in these mice and their offspring.[3,4] Of interest is that these mice developed tumors that closely resembled those seen in neurofibromatosis.[4] One group has reported malignant fibrous histiocytoma, a mesenchymal tumor not dissimilar to those found in neurofibromatosis, developing in a patient with HTLV-I.[5] We suspect that more cases of HTLV-I-associated mesenchymal tumors soon may be reported in the medical literature.

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ABBREVIATIONS USED IN TEXT

ATL = adult T-cell leukemia or lymphoma
ELISA = enzyme-linked immunosorbent assay
HIV = human immunodeficiency virus
HTLV-I = human T-cell lymphotropic virus type I

TABLE 1.—*Human Retroviruses and Their Associated Clinical Syndromes*

Virus	*Associated Syndrome*
Human T-lymphotropic virus type I	Adult T-cell leukemia; tropical spastic paraparesis
Human T-lymphotropic virus type II	Morphologic hairy cell leukemia; cutaneous T-cell malignant neoplasms
Human immunodeficiency virus type I	Acquired immunodeficiency syndrome
Human immunodeficiency virus type II	Acquired immunodeficiency syndrome

Epidemiology

Human T-cell lymphotropic virus type I is endemic in numerous parts of the world. In the continental United States, it is most common in blacks and Native Americans from the southeastern states. In a small survey of healthy blacks from Georgia, the prevalence of HTLV-I antibodies was 2.1%.[6] In Hawaii, HTLV-I seropositivity is found in 20% of immigrants from southern Japan and their offspring but seldom in the white, Chinese, Filipino, or Pacific Islander population.[7,8] It may be expected, however, that with both the increasing frequency of intermarriage among ethnic groups and the increased mobility of our society, we will soon be seeing seropositivity in a broader spectrum of our population.

Several other areas are endemic for HTLV-I: southern Japan, the Caribbean islands, South America, and Africa. Less commonly reported sites include Israel, Taiwan, New Guinea, southern Italy, and the Arctic. Case reports of ATL also have originated from numerous nonendemic locations, although many of these reports involved patients who had immigrated from locations known to be endemic for HTLV-I.

More recently, investigators have found HTLV-I in the intravenous drug user population within the United States, with a prevalence of HTLV-I antibodies reported to range from 7% to 49%.[9-11] Notably, a number of these patients may be coinfected with human immunodeficiency virus (HIV). Whether infection with both agents produces a more aggressive clinical course remains unknown.

Infection with HTLV-I is thought to have occurred first in Africa and then spread to other endemic regions through commercial and slave trading.[12] Further spread has occurred with immigrants and foreign visitors.[13,14] In Hawaii, the virus is thought to have arrived with immigrants from southern Japan.[7,8] While current estimates are that more than a million residents in Japan may be infected with HTLV-I,[15,16] the overall prevalence of seropositivity in the United States is much lower. A blood bank study found that 0.025% of random blood donors in the United States were seropositive for HTLV-I.[17] Using 1988 estimates for the US population,[18] it may be projected that approximately 62,000 Americans are seropositive.

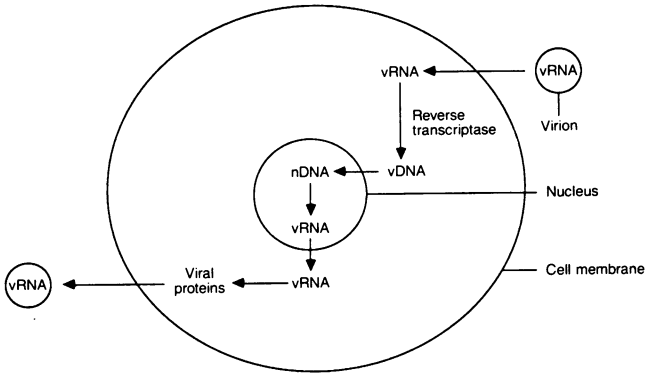

Figure 1.—The life cycle of the HTLV-I virus is shown. nDNA = host nuclear DNA, vDNA = viral DNA, vRNA = viral RNA

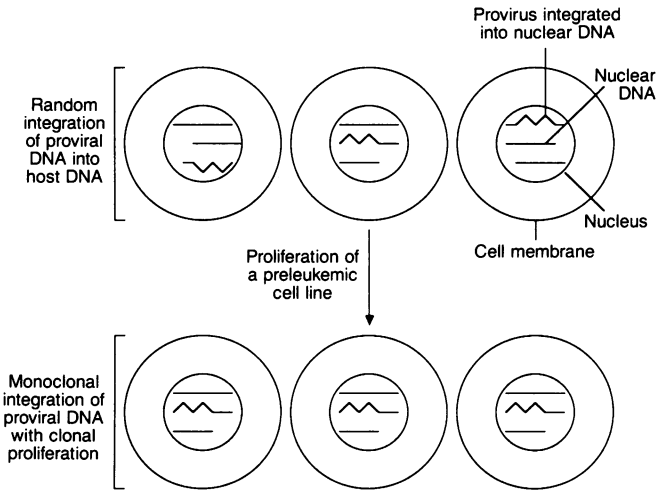

Figure 2.—The schematic shows the progression from polyclonal to monoclonal integration of proviral DNA.

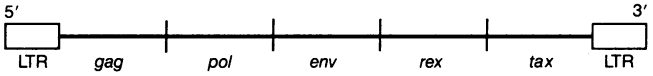

Figure 3.—The HTLV-I proviral genome is shown schematically.

The long terminal repeat (LTR) influences viral transcription, integration, and expression; *gag* encodes for viral core antigens and structural proteins; *pol* encodes for reverse transcriptase; *env* encodes for envelope glycoproteins; *rex* encodes for proteins that regulate *gag* protein synthesis; and *tax* (transactivation factor) encodes for several proteins that can activate distant cellular genes and may also modulate the production of interleukin-2 and its receptor.

Transmission

Several modes of transmission for the HTLV-I virus exist. Vertical transmission from mother to child at birth and transplacental transmission are thought to occur. Sexual intercourse is also a mode of transmission, although seronegativity in spouses of seropositive persons suggests that it is a relatively inefficient means of transmission. These modes account for the often-seen familial clustering of HTLV-I infection.

Breast milk from mothers who are HTLV-I seropositive has been shown to contain HTLV-I-infected lymphocytes.[19] The number of HTLV-I-infected cells in both breast milk and the mother's peripheral blood has been found to correlate with the risk of infection to the breast-feeding child.[20] As

expected, infants born to seropositive mothers and bottle-fed are considerably less likely to display HTLV-I antibodies at the age of 12 months than those who were breast-fed.[21] Breast-feeding is likely the most common mode of transmission of the HTLV-I virus.

Seroconversion can also be found among recipients of cell-containing blood products—erythrocytes, platelets, and leukocyte preparations—from infected donors.[22-25] Seroconversion rates have been reported to be as high as 63%.[22,24] Although no case of transfusion-acquired ATL has yet been reported, a rare progression to tropical spastic paraparesis has been described among recipients of infected blood.

Although the transmission of HTLV-I by insect or parasite vectors has been suggested, insufficient data are available to prove this.[26,27] This mode of transmission continues to be entertained both because of the high overall prevalence of HTLV-I in some endemic areas and because of the higher rates of antibody-positivity encountered with increasing age.

As noted earlier, transmission by contaminated drug paraphernalia occurs in intravenous drug users.[9-11] Because of their unreliability, intravenous drug users represent the greatest risk to our population as a whole. The prevalence of HTLV-I seropositivity may be as high as 47% in these persons,[11] although some of the data may be obscured by the cross-reactivity of HTLV-II in the HTLV-I enzyme-linked immunosorbent assay (ELISA).

Clinical Manifestations

A number of diseases have been associated with HTLV-I infection (Table 2). The most severe of these is acute adult T-cell leukemia or lymphoma. These patients usually have weight loss, lymphadenopathy, hepatosplenomegaly, and, occasionally, lytic bone lesions. Skin lesions from infiltration with leukemic cells may also be seen. The peripheral blood of patients with ATL usually shows leukocytosis with multilobulated lymphocytes. Hypercalcemia is common, and some patients will also have elevated serum bilirubin and lactate dehydrogenase values.[28]

Other patients may have clinical findings more similar to those of non-Hodgkin's lymphoma.[29] The biopsy specimens from these patients will have monoclonal integration of HTLV-I proviral DNA.[28]

A chronic, less symptomatic form of ATL has also been reported. Variably called smoldering or chronic ATL, this form has a fewer number of circulating leukemic cells and often diffuse lymphadenopathy.[28] Although this form of ATL usually follows a more indolent course, these patients must be observed for a progression to acute ATL, with its more aggressive clinical course.

Lastly, a preleukemic state (pre-ATL) has been reported.[30] Patients with this condition are asymptomatic but usually have oligoclonally integrated HTLV-I.[30] About half will develop either smoldering or acute ATL, while the others will remain in a carrier state.[28]

Researchers differ in their estimates as to how often HTLV-I infection will eventually develop into acute ATL. Studies in Japan suggest a lifetime risk of approximately 2%,[31,32] while in the Caribbean the risk before the age of 20 has been estimated to be about 4%.[33] Still other investigators suggest rates of less than 1%.[34,35] When a progression to symptomatic disease does occur, however, it is usually after a latent period lasting many years.

In the past, little therapy has proved beneficial for patients with the acute form of ATL. Neither the leukemic nor the lymphomatous forms of acute ATL respond well to conventional chemotherapy. Recently, however, two groups have reported complete and partial responses to several forms of interferon.[36,37] Whether this will become the treatment of choice in the future awaits clinical trials.

As is evident, HTLV-I infection will never develop into ATL in most patients. They are at risk, however, for several neurologic diseases, including tropical spastic paraparesis, also called HTLV-I associated myelopathy. This is a progressive myelopathy, with patients usually having weakness and sensory findings in the lower extremities and, when the disease is in an advanced stage, urinary incontinence. Spasticity is also a prominent finding in this syndrome. It has a broad age distribution, with a peak occurrence between 40 and 49 years, and appears to be more common in women than in men.[38] Although most often seen in Japan or the Caribbean, cases of tropical spastic paraparesis have also been reported in several locations in the United States (P.S.D.; A.J. Bodner, PhD; M. Okihiro, MD; and colleagues, "HTLV-I and Tropical Spastic Paraparesis in Hawaii," unpublished data, June 1989).[39] Antibodies to HTLV-I have been found in both the serum and cerebrospinal fluid of some patients with this disease.[39-41] Although this is characteristically a progressive, debilitating disease, recent studies have shown patients having symptomatic improvements following a short course of plasmapheresis[42] or corticosteroid therapy.[43]

Additionally, several investigators have suggested an association between HTLV-I and multiple sclerosis; this finding, however, has not been confirmed in subsequent investigations.[44-47] With the use of sophisticated DNA amplification techniques, parts of the viral genome can be detected in some patients with multiple sclerosis, but the significance of these signals is not known. In Jamaica, investigators found HTLV-I antibodies in six patients with an inflammatory polymyositis.[48]

As may be obvious from this discussion, HTLV-I, like

TABLE 2.—*Clinical Syndromes That May Be Associated With Human T-Cell Lymphotropic Virus Type I (HTLV-I) Infection*

Malignant Neoplasms	Neurologic Syndromes	Parasitic Diseases
Adult T-cell leukemia or lymphoma (ATL)	Tropical spastic paraparesis (HTLV-I-associated myelopathy)	Strongyloidiasis
Acute ATL	Mononeuritis	Filariasis
Chronic (smoldering) ATL	Inflammatory polymyositis	Malaria
Others postulated	Others postulated	Others
B-cell chronic lymphocytic leukemia	Multiple sclerosis	Thrombotic thrombocytopenic purpura
Sézary syndrome	Neurofibromatosis	Pulmonary alveolitis
Mycosis fungoides		Chronic inflammatory arthropathy
T-cell non-Hodgkin's lymphoma		Vasculitis
Mesenchymal tumors (?)		

HIV, appears to have a predilection for causing disease of the central nervous system. Although not understood well at this time, this might be either related to direct infection of the neuronal cells or secondary to the immunologic responses to viral infection.

Parasitic diseases, including strongyloidiasis, filariasis, and malaria, have been reported in patients with both asymptomatic HTLV-I carrier states and ATL. All have been suggested as possible cofactors that may affect the clinical course of HTLV-I infection.[28]

Of these parasites, the most extensively studied is strongyloidiasis. Investigators in Japan have reported a higher incidence of HTLV-I antibodies in patients with strongyloidiasis.[49] In Hawaii, an area not endemic for *Strongyloides stercoralis,* we, too, have found both ATL and HTLV-I seropositivity in several patients with strongyloidiasis.[50] In Okinawa, Nakada and colleagues have noted monoclonal integration of HTLV-I more frequently in patients with strongyloidiasis than in those without.[51] This has led them to suggest that *Strongyloides stercoralis* may play a role in the leukemogenesis of this virus.[51] Whether this in fact occurs remains unknown.

We have recently reported a case of thrombotic thrombocytopenic purpura in a patient seropositive for HTLV-I.[52] While there have been several reports of this disease in patients with HIV infection,[53-56] it had not previously been associated with HTLV-I. Additional studies will be needed before any conclusive association between these two disorders can be established, however.

It appears likely that other clinical conditions resulting from infection with HTLV-I will be reported as our experience with this virus becomes more widespread. Unfortunately, at the current time no treatment is available for those with asymptomatic infections. Consequently, the knowledge of a person's antibody status is only helpful from a preventive point of view. Perhaps in the future drugs such as azidothymidine, used for the treatment of patients infected with HIV, will be found useful for treating HTLV-I infection. Early studies suggest some in vitro activity of this drug and others against HTLV-I.[57,58] Clearly, preventing the spread of the HTLV-I virus is one area where we currently can make the greatest contribution to reducing the risks of this infection.

Preventive Measures

At the present time the burden of responsibility for treating and preventing HTLV-I infection and its associated clinical syndromes lies with those who care for patients from the populations at risk for acquiring this infection. In the United States this includes all who live in the southeastern states; those with southern Japanese ancestry; immigrants from Africa, the Caribbean islands, Japan, and Central and South America; and intravenous drug users who share needles. In addition, the spouses, children, and families of patients from these groups are at risk for acquiring HTLV-I infection. As one can immediately see, a large part of the American population may be at risk for exposure to HTLV-I.

Several approaches can be used to reduce the rate at which HTLV-I is spread (Table 3). Many of these hinge on first discerning those persons who are already infected. Several methods currently exist (Table 4). An ELISA assay, which is both sensitive and specific, was approved by the Food and Drug Administration in 1988 and is in routine use for screening donor blood for HTLV-I antibodies.[38] This step may be expected to reduce substantially the prevalence of transfusion-acquired HTLV-I infection, particularly in endemic locations.

TABLE 3.—*Methods That Could Be Employed to Reduce Transmission of Human T-Cell Lymphotropic Virus Type I*

Means of Transmission	*Method of Prevention*
Blood transfusion	Screening of donor blood supply
Childbirth	Screening of mothers at risk and discouraging them from breast-feeding
Sexual intercourse	Using condoms
Intravenous drug paraphernalia	Discouraging the sharing of needles and identifying seropositive drug users

TABLE 4.—*Tests Available for Identifying Human T-Cell Lymphotropic Virus Type I (HTLV-I) Viral Infection*

Test	*Comment*
ELISA (enzyme-linked immunosorbent assay)*	Rapid screening test; inexpensive; cannot distinguish HTLV-I from HTLV-II
RIA (radioimmunologic assay)	Confirmatory
Western blot	Confirmatory
Polymerase chain reaction	Confirmatory; minimal tissue needed, but subject to contamination
Virus culture	Difficult; time-consuming; expensive

*Currently used for the screening of the blood supply in the United States.

Although confirmatory tests for HTLV-I exist, they have not yet been approved by the Food and Drug Administration. When they become readily available, both the Western blot assay and the polymerase chain reaction[59,60] will be useful confirmatory tests.

Despite the lack of therapy for HTLV-I infection, the knowledge of a patient's antibody status could be used to substantially reduce the rate of spread of this virus. Mothers who test positive for HTLV-I should be instructed not to breast-feed their infants. The use of condoms can be expected to reduce the spread of virus among persons engaging in sexual intercourse with an infected partner. The sharing of needles should be discouraged among intravenous drug users, to prevent not only HTLV-I but also infection with HIV and the hepatitis B virus.

Increasing attention has been given to the use of autologous transfusion because HIV infection has entered the realm of transfusion-associated diseases. Autologous transfusions can reduce the rates of multiple infectious processes, including HTLV-I, HIV, hepatitis B, non-A, non-B hepatitis, and cytomegalovirus, as well as some noninfectious processes such as transfusion reactions. The use of autologous transfusions should be encouraged and programs should be instituted in centers where this procedure is not already being done. The effect of these programs on the transmission of HTLV-I will likely be small, however, now that routine screening for antibody in the donor blood supply has commenced.

Future Efforts

An improved understanding of the HTLV-I virus is necessary before we will be able to substantially alter its course in humans. The mechanisms of leukemogenesis, determi-

nants of viral latency and activation, and the process by which neurologic dysfunction is induced all are important areas of research. Ongoing studies include efforts to delineate how the *tax* gene promotes rapid cellular growth and what role this plays in the progression from an asymptomatic carrier state to overt ATL or tropical spastic paraparesis. Investigators also are looking for a method to follow proviral integration from a polyclonal state to monoclonality and, therefore, to ATL. This capability would allow earlier and possibly more effective therapy for this aggressive disease.

Clinical studies are also sorely needed. A thorough knowledge of the natural history of viral infection will be necessary to help guide subsequent therapeutic trials. These likely will include pharmacotherapy with drugs such as azidothymidine or the interferons for ATL, and corticosteroids or plasmapheresis for tropical spastic paraparesis.

Although a number of diseases have already been related to the HTLV-I virus, physicians in endemic locations should be looking for as-yet-unknown processes that may also be related to this virus. Diseases such as the vasculitides and peripheral nerve palsies are possibilities.

Rapid, inexpensive, and accurate assays for HTLV-I will need to be developed and made accessible to clinicians. Although the currently available ELISA assay is both rapid and inexpensive, concern exists that it may not adequately differentiate HTLV-I from HTLV-II. The extent to which HTLV-II has been masquerading as HTLV-I in previous studies is therefore unknown.

Lastly, as with HIV, our ultimate goal will continue to be to produce a safe and effective vaccine to prevent an initial infection with this virus. The highly conserved and stable nature of HTLV-I may make a vaccine a more achievable goal and therefore may serve as a model for developing an HIV vaccine.

Conclusion

By a concerted effort from those physicians who care for patients in the groups at high risk for HTLV-I infection and those involved in basic scientific research, it is hoped that a rapid resolution to the increasing prevalence of HTLV-I infection in the United States can be achieved. The greatest reservoirs remain those groups in whom the virus is endemic. Preventing transmission by these groups—most importantly to their offspring—remains our greatest opportunity to reduce the spread of this virus. The recent institution of HTLV-I antibody screening in donated blood should help somewhat. Ongoing efforts to educate physicians and patients about this disease should have a notable effect on preventing HTLV-I infection and its concomitant diseases.

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Book Review

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

Clinical Imaging—An Introduction to the Role of Imaging in Clinical Practice

Edited by Matthew Freedman, MD, Associate Professor of Diagnostic Radiology, Georgetown University School of Medicine; Associate Professor of Diagnostic Radiology, Johns Hopkins University School of Medicine; and Associate Professor of Diagnostic Radiology and Assistant Professor of Orthopedic Surgery, University of Maryland School of Medicine, Baltimore. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1988. 589 pages, $45.

This book is intended for use as the text in a three- to five-week radiology clinical clerkship course. The text begins with a chapter that discusses methods for analyzing imaging studies. In chapters 2 through 6 methods used for imaging the body are discussed. Chapters 7 through 62 cover the clinical applications of the imaging methods, divided by anatomic region, and the final chapter outlines medical economics and the effect of diagnostic imaging on the cost of health care.

The book is printed on good quality, 8½ × 11 paper with a large print size. Many pages are blank or have only a few lines of print.

Although the image quality of some of the illustrations is excellent, that is, unfortunately, not a uniform characteristic of the text. Many of the chest images, for example, are reproduced too dark, so that pulmonary vessels are not distinct. Most of the ultrasound and computed tomographic images are not of the high quality that is obtainable with state-of-the-art technology. Very few magnetic resonance (MR) images are included, with only a few MR images of the brain or spinal cord, areas in which MR has revolutionized our diagnostic ability. When MR images are shown, there is not an explanation of T1 and T2 relaxation values, something a medical student might be expected to know. Some of the captions of the illustrations are inadequate in that they fail to give the diagnosis or they refer the reader to the text. There are no color illustrations of Doppler or of gross or microscopic pathology for correlation, as there are in Lucy Squires's textbook for medical students. Several important entities are not discussed at all or are mentioned only in passing: Wilms's tumor, neuroblastoma, osteogenic sarcoma, leukemia, congenital heart disease, and congenital dislocation of the hip.

Aside from these deficiencies, however, there is much in the book to make it valuable to medical students. Specifically, I found the organization of each chapter to be attractive and practical. The key concepts are presented, the objectives are enumerated, the entity is discussed and illustrated, the findings are summarized, review questions are provided, a vocabulary of new words is listed, and, finally, there are suggestions for further reading.

I think that medical students will find that this book is a very palatable introduction to clinical radiology. The interested student will use this book as a stepping stone to read, in depth, other current radiology textbooks oriented either toward organ systems or new imaging technologies.

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